

## Beta-lactam antibiotics

Penicillins

Target - Cell wall - interfere with cross linking  
Actively growing cells

Bind to **Penicillin Binding Proteins**

**Enzymes involved in cell wall synthesis**

## Activity of an Antibiotic

Affinity for target

Permeability properties  
(ability to get to the target)

Stability to bacterial enzymatic degradation

### Bacterial modifications:

- 1 – Mutate target - ? More than one protein  
Importance of the target –  
? Essential
2. Permeability – Size/charge considerations  
? Substrate for an efflux pump
3. Selection for mutants that destroy the antibiotic

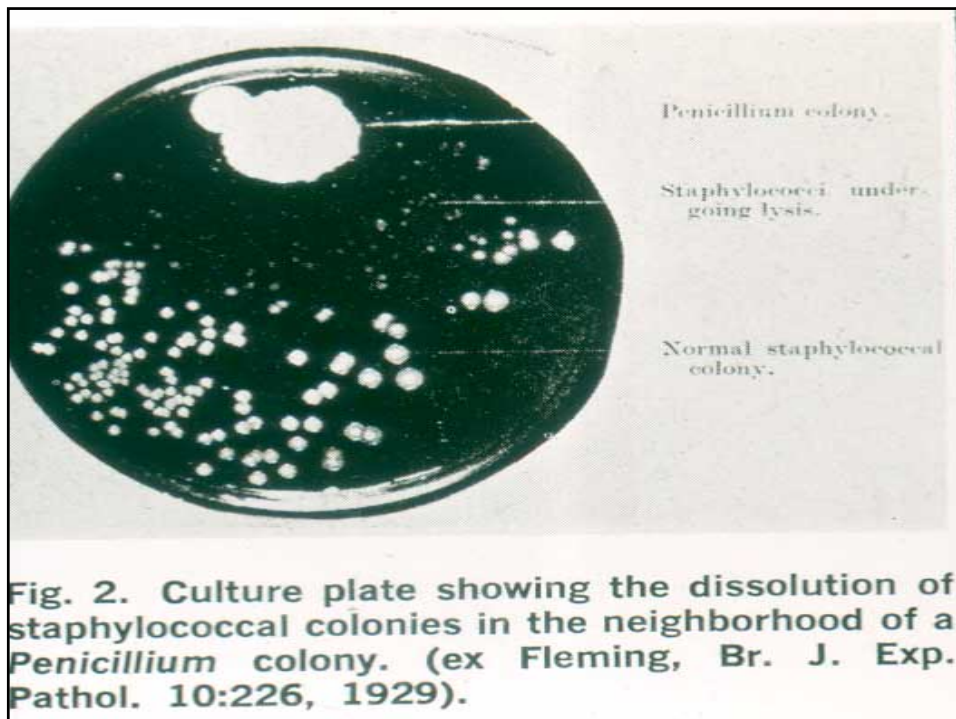
WHO discovered the penicillins??

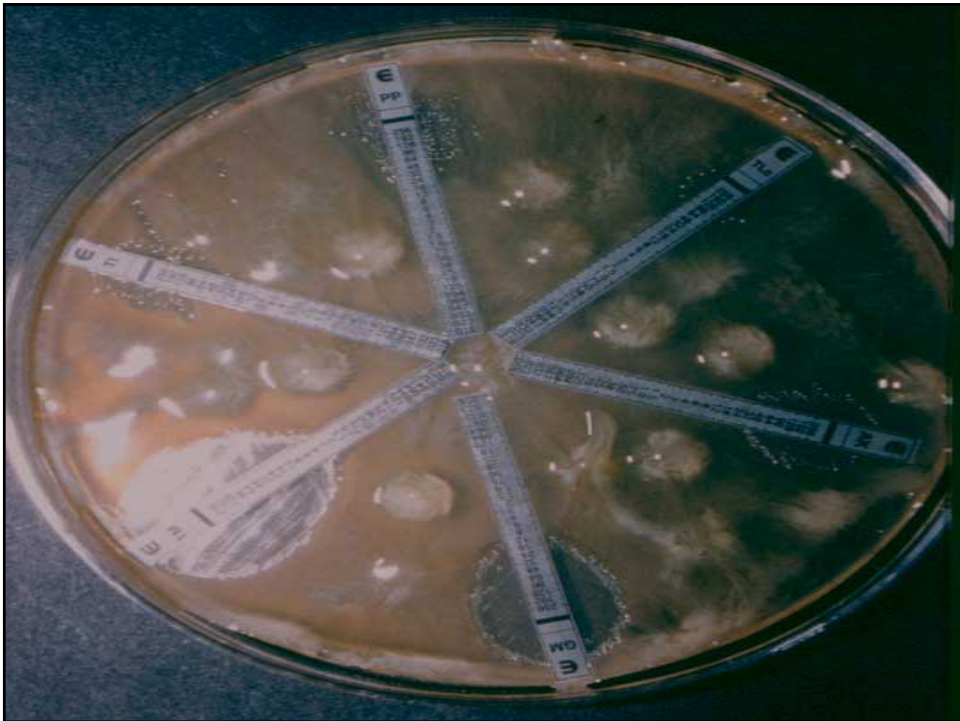
Abess Hildegarde von Bingen ?

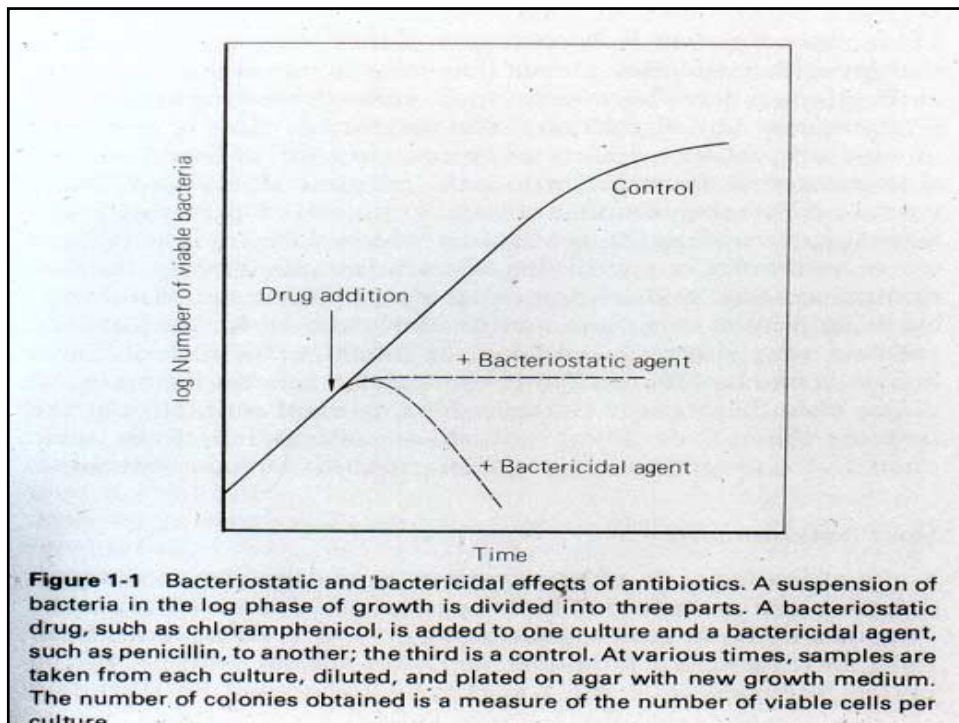
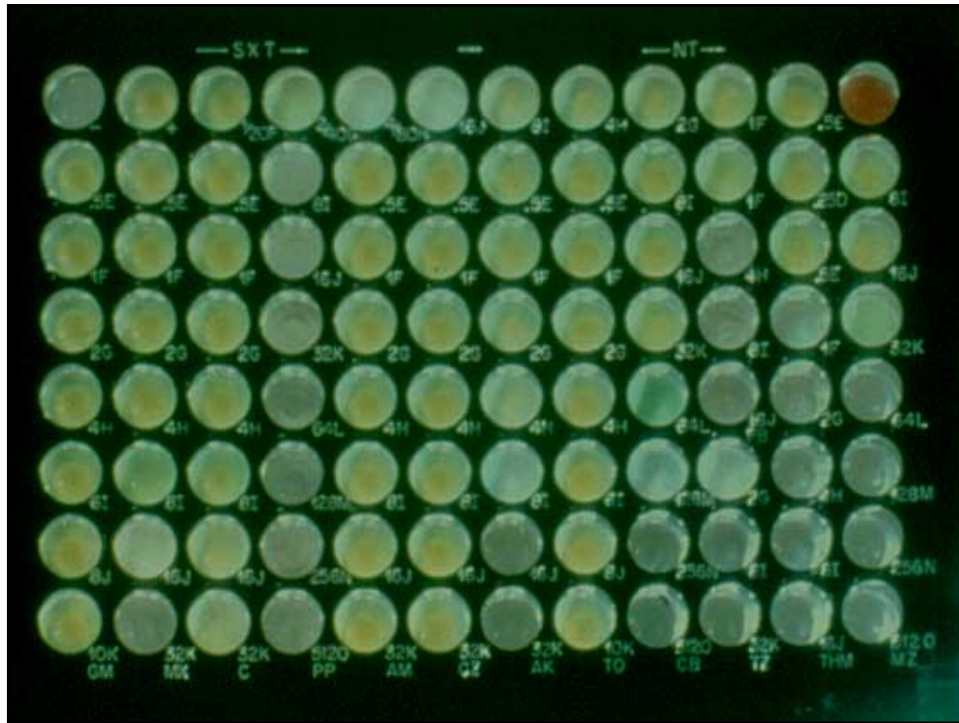
“Good things that grow on the sides of trees...”

Fleming –

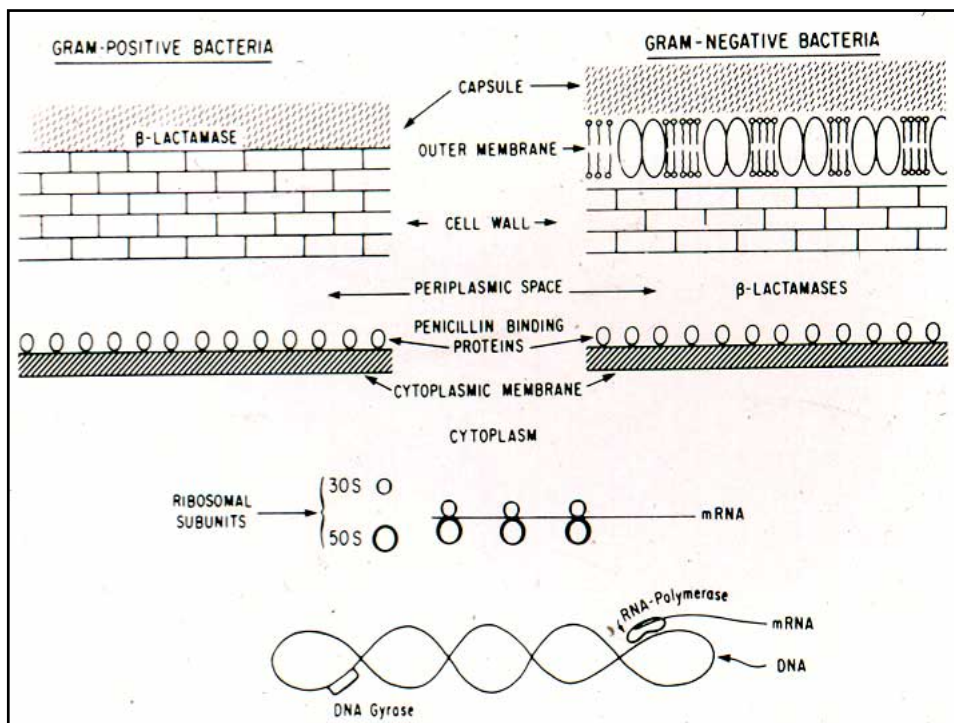
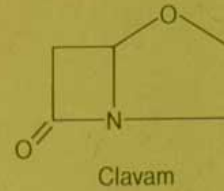
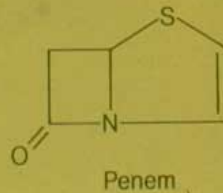
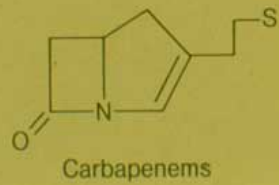
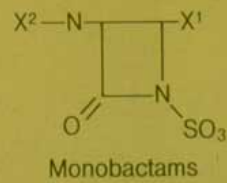
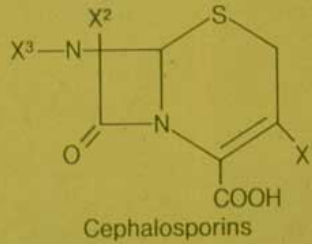
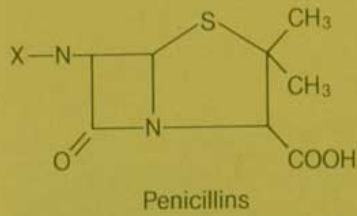
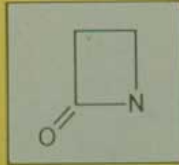
Florey – WWII....







# What Is a $\beta$ -Lactam?



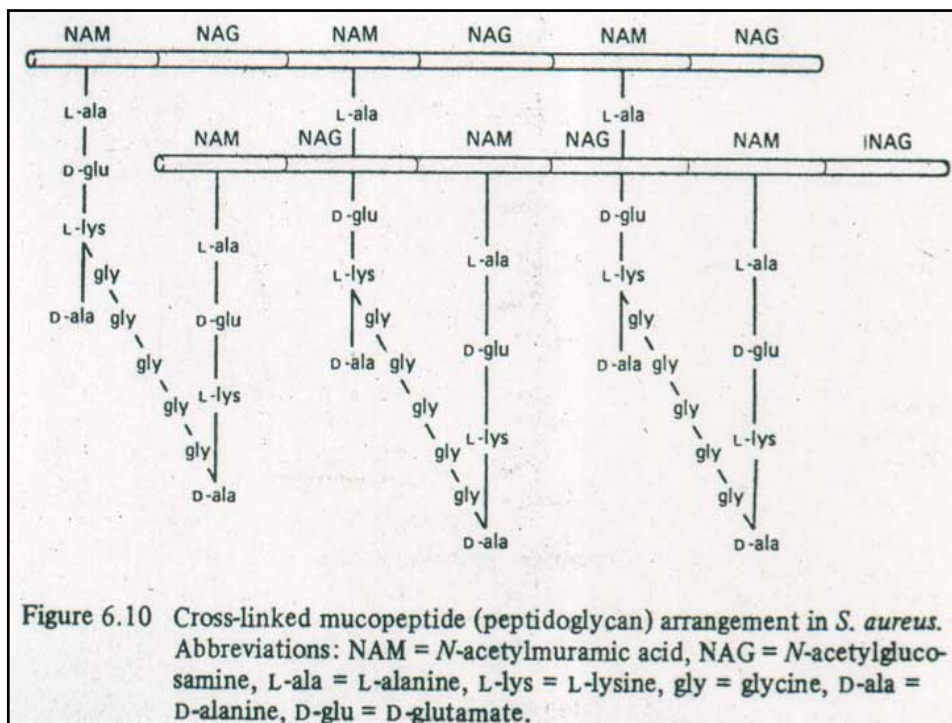
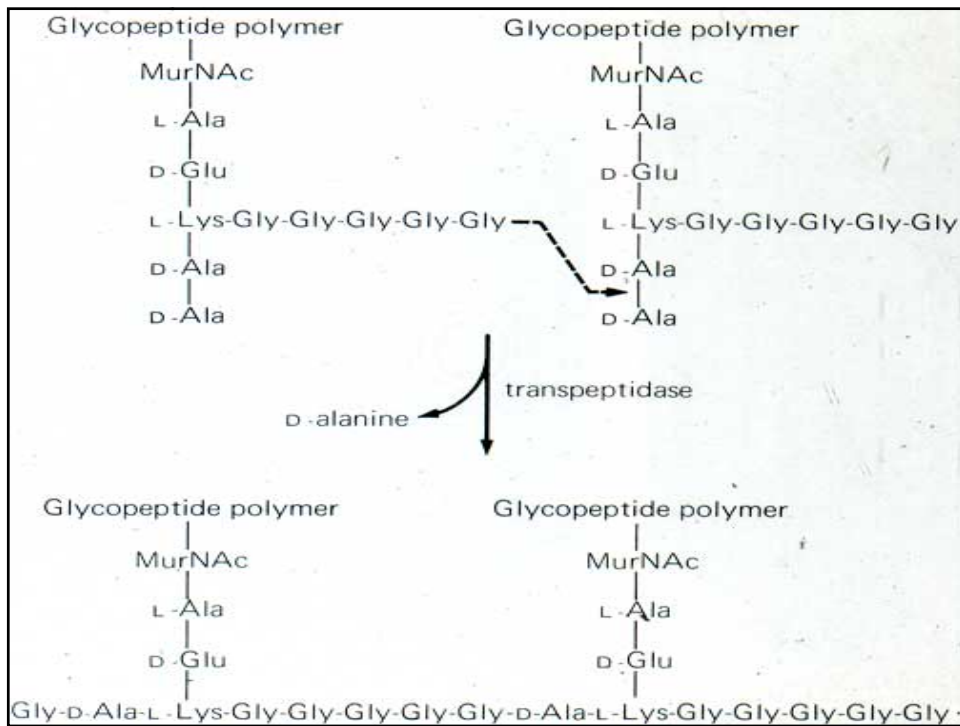


Figure 6.10 Cross-linked mucopeptide (peptidoglycan) arrangement in *S. aureus*. Abbreviations: NAM = *N*-acetylmuramic acid, NAG = *N*-acetylglucosamine, L-ala = L-alanine, L-lys = L-lysine, gly = glycine, D-ala = D-alanine, D-glu = D-glutamate.

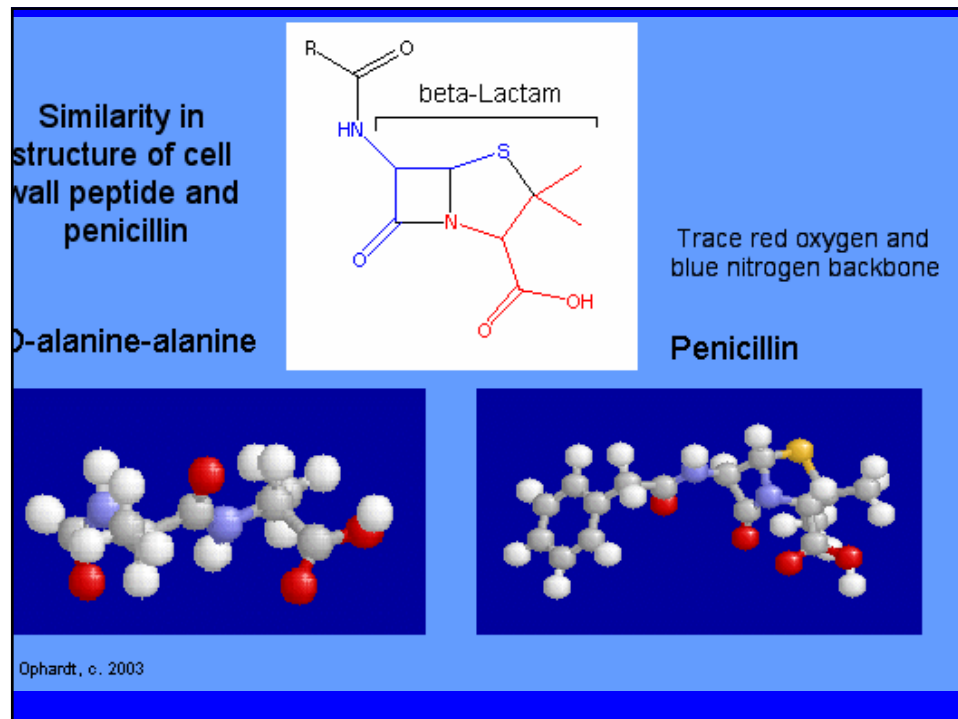
## Penicillin binding proteins

Transpeptidases

Carboxypeptidases

Differ in Gram (+) and in Gram (-) bacteria

Differ in abundance



Ophardt, c. 2003

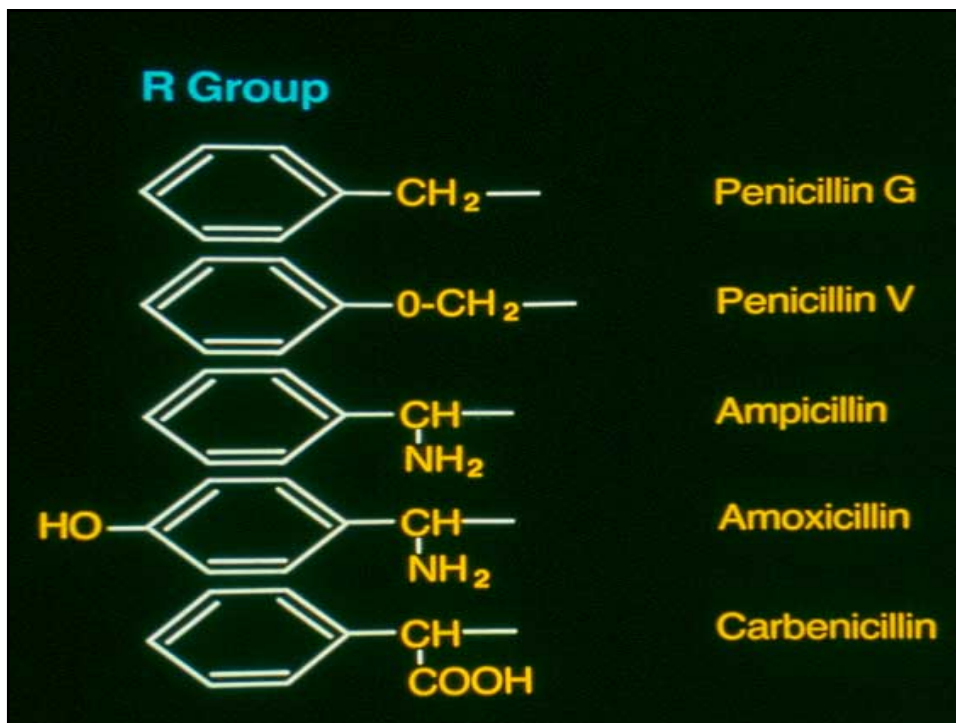


## Activity of the beta-lactam antibiotic:

Affinity for critical PBP's (number of copies of the target)

Ability to get to the target (permeability properties –  
more of an issue for Gram negs)

Stability to beta-lactamases - degradation



**Beta-lactamases** - cleave the beta-lactam ring -  
inactivate the drug -  
Open ring - can't bind to the target

Co-evolved with the penicillin binding proteins

Share a ser-X-X-lys - binding site for interactions

Gram positives - Secreted into the environment

Gram negatives - Secreted into the periplasmic space

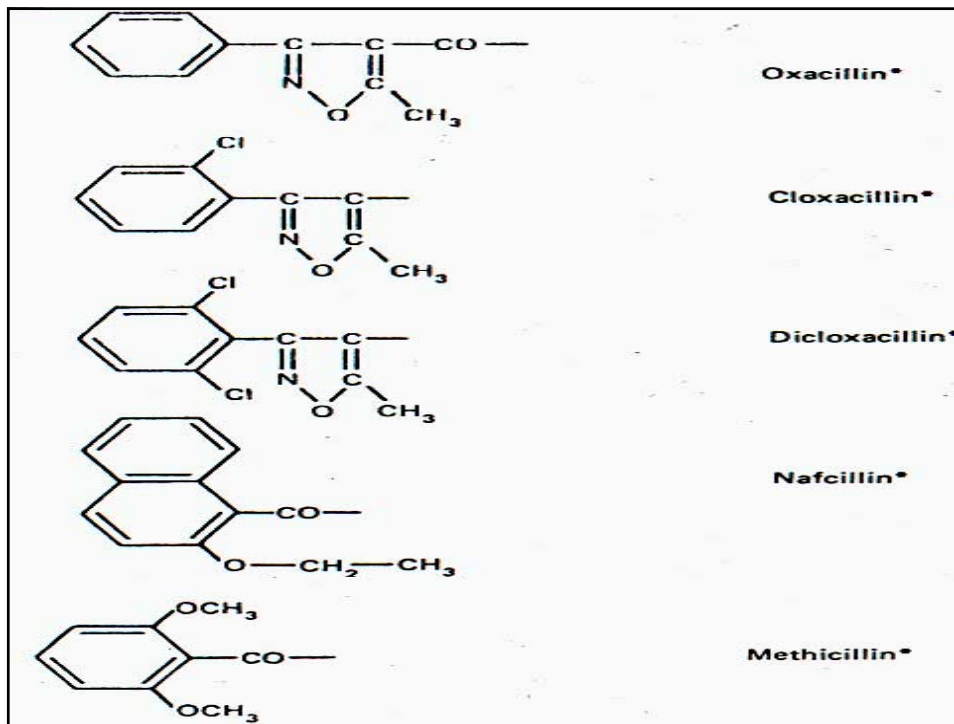
### ANTI-staphylococcal penicillins

“semi-synthetic”

Add bulky side chains to provide

STERIC HINDRANCE to protect the  
Beta-lactam nucleus –

Gram positives – secrete bla's – “cloud”



### Anti-staphylococcal penicillins

Strategy - Add a bulky side group to block beta-lactamase

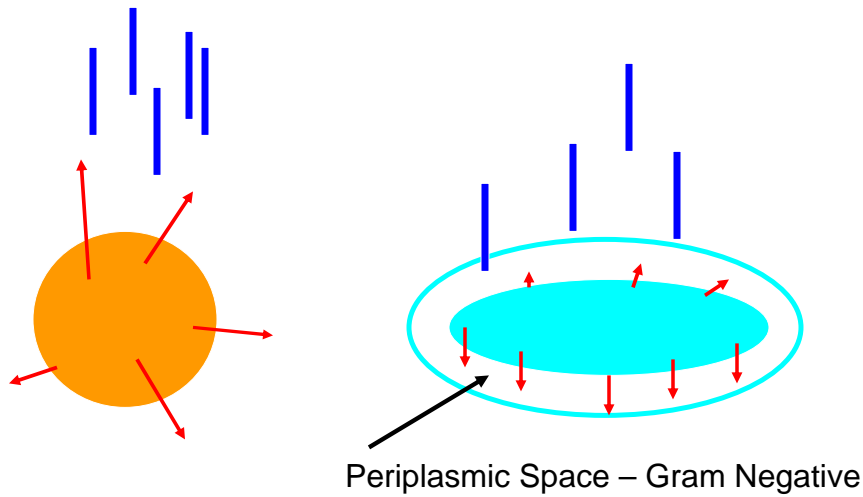
(Methicillin) - renal toxicity

Nafcillin

Oxacillin

Cloxacillin (di-clox) - oral drugs

### Beta-lactamase secretion in Gram positive and Gram negative bacteria



Capsule – No barrier

Peptidoglycan – No barrier

Outer wall – Porins Control access

Cytoplasmic Membrane – Lipid Bilayer

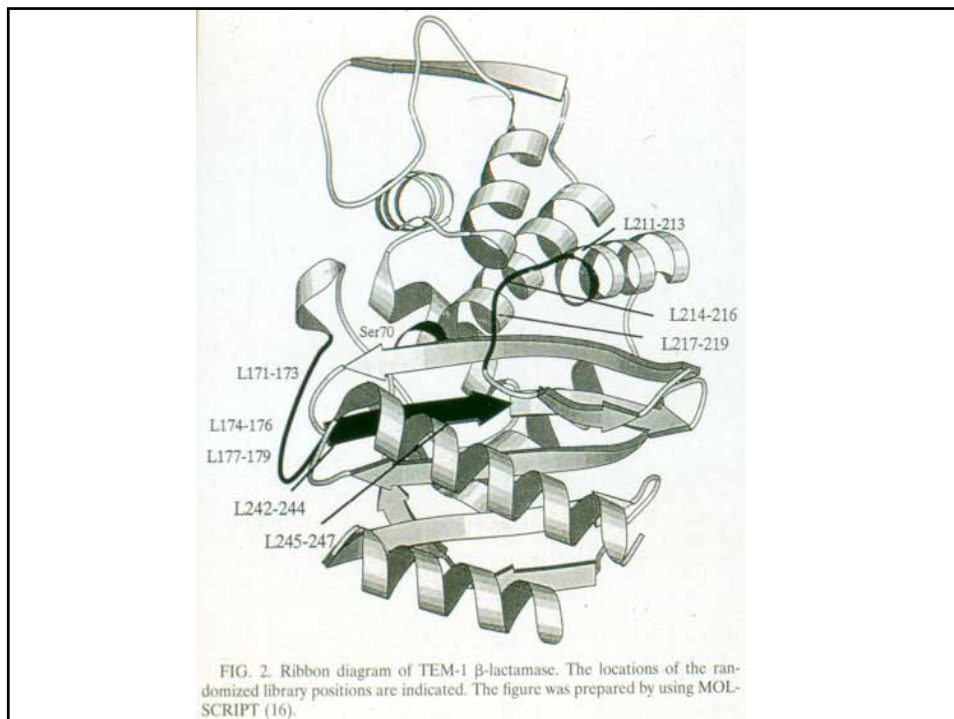
## Beta-lactamases

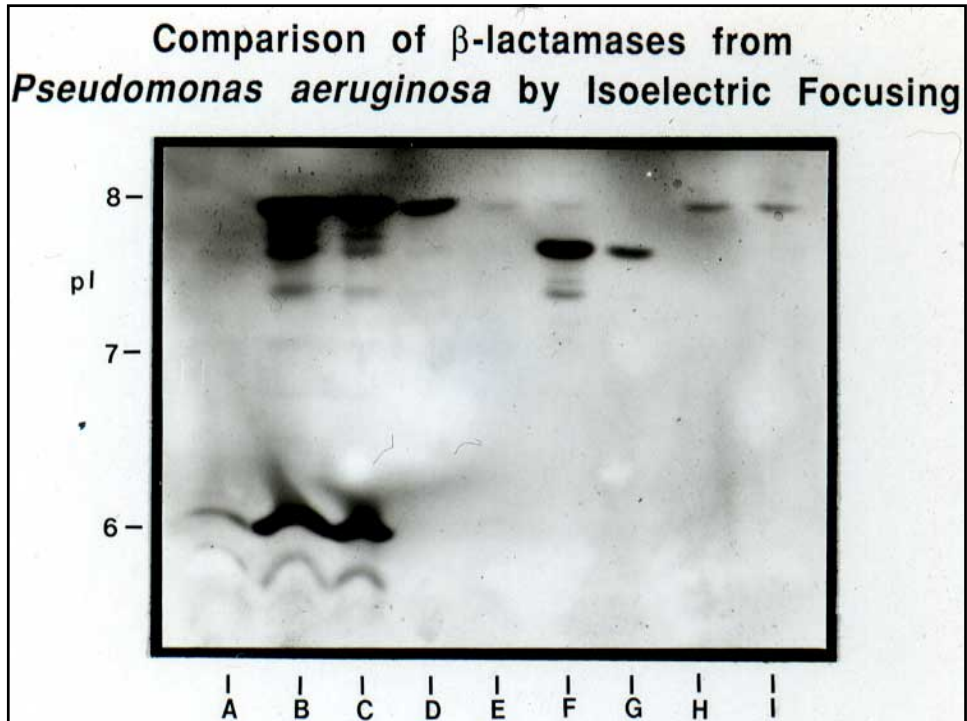
Regulation - Constitutive - Chromosomal (*E.coli*)

Plasmid mediated -  
copy number dependent

**Inducible** - chromosomal - SPACE  
organisms - as a model

2-component signaling - (*ampD*, *ampE*, *ampR*)  
Sensor  
Response regulator  
Transcriptional activator





**Drugs in clinical use:**

Penicillin G, VK

Ampicillin (+) clavulanic acid (beta-lactamase inhibitor)

(oral or parenteral)

Piperacillin - anti-*Pseudomonas* (+tazobactam)

(parenteral)

Spectrum - gram positive and gram negative -

Not inherently beta-lactamase stable

Spectrum - dependent upon permeability properties

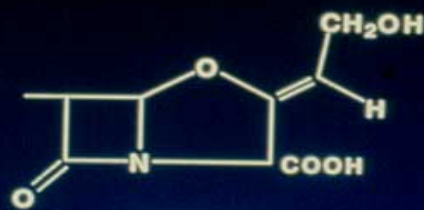
### Add a beta-lactamase inhibitor

Clavulanic acid -  
Sulbactam  
Tazobactam

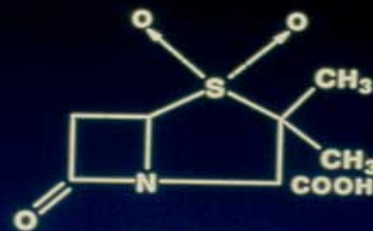
Expands spectrum of activity  
Anaerobes

NOT effective against the beta-lactamases of the  
SPACE organisms

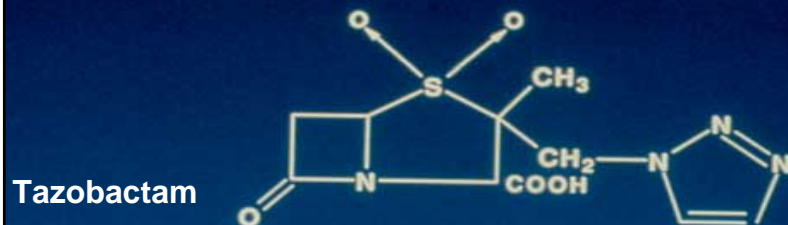
### $\beta$ -LACTAMASE INHIBITORS



Clavulanate

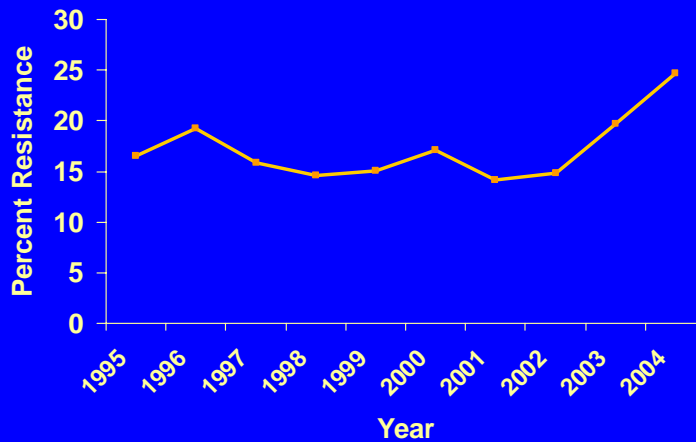


Sulbactam



Tazobactam

### 3<sup>rd</sup> generation cephalosporin-resistant *Klebsiella pneumoniae* Among ICU Patients, 1995-2004



Source: National Nosocomial Infections Surveillance (NNIS) System

### Pharmacology of the penicillins

Absorption - Amoxicillin - acid stable  
dosing - give more - longer intervals  
Augmentin - amox + clav - diarrhea

Metabolism - minor

Excretion - Renal - tubular secretion  
Increase serum levels with probenecid  
Biliary - only ureido penicillins  
Nafcillin

Distribution - Anions - charged - extracellular space  
CSF - with inflammation  
Concentrated in urine